

Powder study of hydrochlorothiazide–
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Key indicators

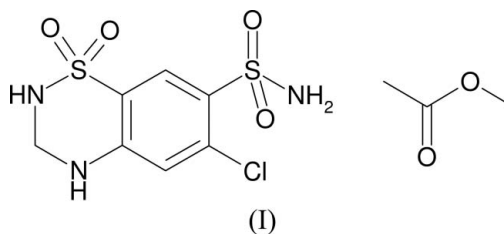
Powder X-ray study
 $T = 298\text{ K}$
Mean $\sigma(\text{C}-\text{C}) = 0.002\text{ \AA}$
 R factor = 0.013
 wR factor = 0.018
Data-to-parameter ratio = 3.41For details of how these key indicators were
automatically derived from the article, see
<http://journals.iucr.org/e>.

A polycrystalline sample of the title compound, $\text{C}_7\text{H}_8\text{ClN}_3\text{O}_4\text{S}_2 \cdot \text{C}_3\text{H}_6\text{O}_2$, was produced during an automated parallel crystallization search on hydrochlorothiazide (HCT). The crystal structure was solved by simulated annealing from laboratory X-ray powder diffraction data collected at room temperature to 1.75 \AA resolution. Subsequent Rietveld refinement yielded an R_{wp} value of 0.0182 to 1.54 \AA resolution. The compound crystallizes with one molecule of HCT and one of methyl acetate in the asymmetric unit and displays an extensive hydrogen-bonding network.

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Comment

Hydrochlorothiazide (HCT) is a thiazide diuretic which is known to crystallize in at least two non-solvated forms; form I (Dupont & Dideberg, 1972) and form II (Florence *et al.*, 2005). During an automated parallel crystallization search on HCT, multi-sample X-ray powder diffraction analysis (Florence *et al.*, 2003) of all recrystallized samples revealed a novel pattern which was identified as the methyl acetate solvate (I).



The crystal structure of (I) was solved by simulated annealing using laboratory X-ray powder diffraction data. The compound crystallizes in the space group $P2_1/c$ with one molecule of hydrochlorothiazide (HCT) and one of methyl acetate in the asymmetric unit (Fig. 1). In (I), the six-membered ring N2/S1/C1/C2/N1/C3 in HCT displays a non-planar conformation, atom N2 having the largest deviation [$0.646(2)\text{ \AA}$] from the least-squares plane through the aromatic ring. The sulfonamide side chain displays a torsion angle N3–S2–C5–C6 of $65.1(4)^\circ$, such that atom O1 eclipses H4, and atoms O4 and N3 are staggered with respect to Cl1.

The crystal packing (Fig. 2) is stabilized by intermolecular N–H \cdots O hydrogen bonds (Table 2), which form a centrosymmetric $R_2^2(8)$ dimer motif between HCT molecules (Fig. 3, top), and an $R_4^4(24)$ motif interconnecting two molecules of HCT and two molecules of solvent (Fig. 3, bottom). In addition, adjacent HCT molecules are connected by a C–H \cdots O interaction (Table 2).

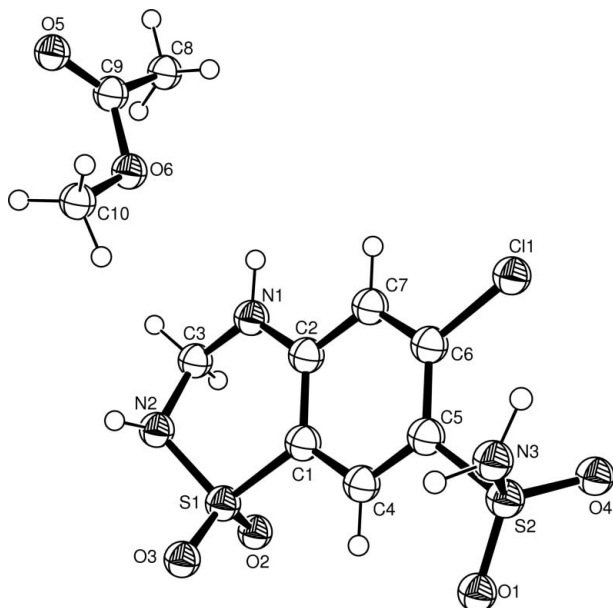


Figure 1
The atomic arrangement in (I), showing the contents of the asymmetric unit and the atom-numbering scheme. Isotropic displacement ellipsoids are shown at the 50% probability level.

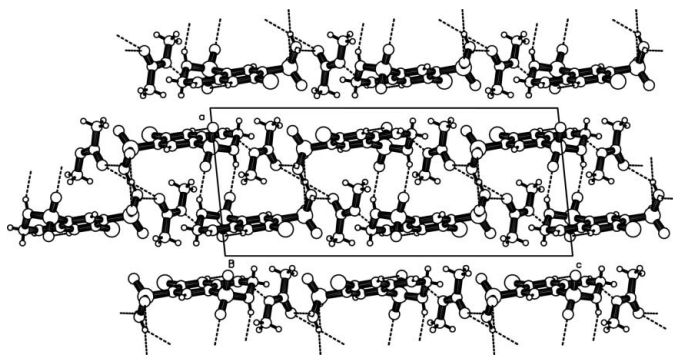


Figure 2
The crystal structure of (I), viewed along the *b* axis. Dashed lines indicate hydrogen bonds.

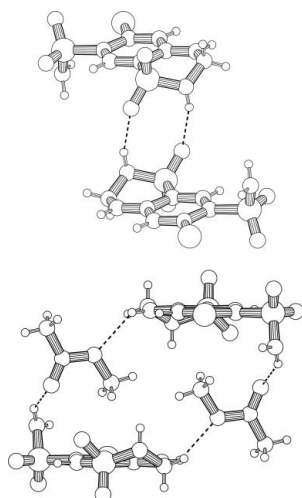


Figure 3
The $R_2^2(8)$ (top) and $R_4^4(24)$ (bottom) hydrogen-bonded motifs within the structure of (I).

Hydrophobic interactions within the structure of (I) include a C–H··· π approach between C10–H10A and the centroid of the ring C1/C2/C4–C7 [C10···centroid distance of 3.364 (2) Å]. The structure also contains a short O···C intermolecular contact of 2.915 (4) Å between atom O1 of the HCT sulfonamide side chain and C9ⁱ [symmetry code: (i) $x, \frac{3}{2} - y, -\frac{1}{2} + z$], the carbonyl C atom of methyl acetate. This type of contact is not unique, and a search of the Cambridge Structural Database (Version 5.26; Allen, 2002) for (O)S=O···C=O(ester) intermolecular contacts less than the sum of the van der Waals radii yielded 38 structures comprising 41 contacts within the range 2.83–3.21 Å. It is reasonable to consider this contact to be an attractive dipole–dipole interaction of the type S=O(δ^-)···C(δ^+)=O, similar to those described elsewhere for carbonyl–carbonyl interactions (Allen *et al.*, 1998).

Experimental

A polycrystalline sample of (I) was recrystallized by cooling a saturated methyl acetate–acetone (50:50) solution from 313 to 283 K. The sample was lightly ground in a mortar, loaded into a 0.7 mm borosilicate glass capillary and mounted on the diffractometer. Data were collected from a sample in a rotating 0.7 mm borosilicate glass capillary using a variable count time scheme (Shankland *et al.*, 1997; Hill & Madsen, 2002).

Crystal data

$C_7H_8ClN_3O_4S_2 \cdot C_3H_6O_2$
 $M_r = 371.83$
 Monoclinic, $P2_1/c$
 $a = 9.39703$ (16) Å
 $b = 7.28424$ (16) Å
 $c = 21.9483$ (3) Å
 $\beta = 95.8020$ (11)°
 $V = 1494.67$ (6) Å³
 $Z = 4$

$D_x = 1.652$ Mg m⁻³
 Cu $K\alpha_1$ radiation
 $\mu = 5.20$ mm⁻¹
 $T = 298$ K
 Specimen shape: cylinder
 $12 \times 0.7 \times 0.7$ mm
 Specimen prepared at 298 K
 White

Data collection

Bruker AXS D8 Advance diffractometer
 Specimen mounting: 0.7 mm borosilicate capillary
 Specimen mounted in transmission mode
 Scan method: step

430 measured reflections
 $h = 0 \rightarrow 6$
 $k = -4 \rightarrow 4$
 $l = -14 \rightarrow 14$
 $2\theta_{\min} = 5.0$, $2\theta_{\max} = 60.0^\circ$
 Increment in $2\theta = 0.014^\circ$

Refinement

Refinement on I_{net}
 $R_p = 0.013$
 $R_{wp} = 0.018$
 $R_{\text{exp}} = 0.013$
 $R_B = 0.007$
 $S = 1.45$
 Excluded region(s): 5.0 to 7.5 due to high low angle background and the absence of Bragg reflections.
 Wavelength of incident radiation: 1.5406 Å
 Profile function: fundamental parameters with axial divergence correction

430 reflections
 126 parameters
 Only H-atom coordinates refined
 $w = 1/\sigma(Y_{\text{obs}})^2$
 $(\Delta/\sigma)_{\max} = 0.004$
 $\Delta\rho_{\max} = 0.6$ e Å⁻³
 $\Delta\rho_{\min} = -0.7$ e Å⁻³
 Preferred orientation correction: A spherical harmonics-based preferred orientation correction (Järvinen, 1993) was applied with TOPAS during the Rietveld refinement.

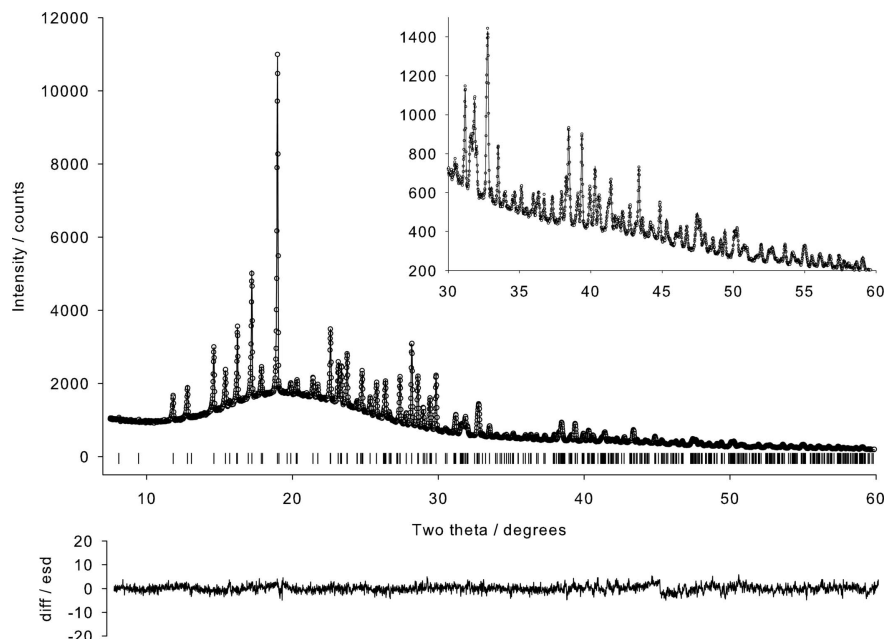


Figure 4 Final observed (points), calculated (line) and difference $[(y_{\text{obs}} - y_{\text{calc}}) / \sigma(y_{\text{obs}})]$ profiles for the Rietveld refinement of the title compound.

Table 1 Selected geometric parameters (\AA , $^\circ$).

C1—C6	1.729 (3)	S2—C5	1.773 (2)
S1—O2	1.426 (3)	O5—C9	1.229 (3)
S1—O3	1.424 (3)	O6—C9	1.379 (3)
S1—N2	1.647 (2)	O6—C10	1.432 (3)
S1—C1	1.770 (2)	N1—C2	1.364 (2)
S2—O1	1.430 (3)	N1—C3	1.395 (2)
S2—O4	1.425 (4)	N2—C3	1.442 (2)
S2—N3	1.635 (2)		
O2—S1—O3	122.3 (2)	S1—N2—C3	114.00 (13)
O2—S1—N2	105.1 (2)	S1—C1—C4	119.05 (13)
O2—S1—C1	108.82 (19)	S1—C1—C2	119.79 (11)
O3—S1—N2	108.26 (19)	N1—C2—C7	120.31 (16)
O3—S1—C1	109.26 (19)	N1—C2—C1	121.89 (15)
N2—S1—C1	100.99 (11)	N1—C3—N2	112.9 (2)
O1—S2—O4	117.9 (3)	S2—C5—C4	117.37 (16)
O1—S2—N3	109.7 (3)	S2—C5—C6	124.82 (16)
O1—S2—C5	106.0 (2)	C11—C6—C7	116.92 (19)
O4—S2—N3	108.3 (2)	C11—C6—C5	121.60 (16)
O4—S2—C5	108.99 (19)	O5—C9—O6	117.66 (19)
N3—S2—C5	105.25 (16)	O5—C9—C8	129.20 (18)
C9—O6—C10	117.19 (17)	O6—C9—C8	113.14 (14)
C2—N1—C3	123.80 (15)		

Table 2 Hydrogen-bond geometry (\AA , $^\circ$).

$D-H \cdots A$	$D-H$	$H \cdots A$	$D \cdots A$	$D-H \cdots A$
N1—H1 \cdots O6	0.94 (1)	2.48 (1)	3.052 (4)	119 (1)
N2—H2 \cdots O3 ⁱ	0.95 (1)	2.17 (1)	3.086 (3)	161 (1)
N3—H31 \cdots O1 ⁱⁱ	0.95 (1)	2.46 (1)	2.967 (6)	113 (1)
N3—H31 \cdots O5 ⁱⁱⁱ	0.95 (1)	2.26 (1)	3.090 (3)	146 (1)
N3—H32 \cdots O5 ^{iv}	0.95 (1)	2.12 (1)	2.960 (4)	147 (1)
C7—H7 \cdots O2 ^v	0.95 (1)	2.41 (1)	3.336 (4)	165 (1)

Symmetry codes: (i) $-x + 1, -y + 2, -z$; (ii) $-x + 1, +y - \frac{1}{2}, -z - \frac{1}{2}$; (iii) $-x + 1, -y + 1, -z$; (iv) $x, -y + \frac{1}{2}, +z - \frac{1}{2}$; (v) $x, y - 1, z$.

The diffraction pattern indexed to a monoclinic cell [$M(20) = 34.0$, $F(20) = 81.2$; *DICVOL-91*; Boulitif & Louer, 1991] and the space group $P2_1/c$ was assigned from volume considerations and a statistical consideration of the systematic absences (Markvardsen *et al.*, 2001). The data set was background subtracted and truncated to $52.2^\circ 2\theta$ for Pawley fitting (Pawley, 1981; $\chi^2_{\text{Pawley}} = 1.64$) and the structure solved using the simulated annealing (SA) global optimization procedure, described previously (David *et al.*, 1998), that is now implemented in the *DASH* computer program (David *et al.*, 2001). The internal coordinate descriptions (including H atoms) of the molecules were constructed from standard bond lengths, angles and torsions where appropriate. The structure was solved using data to $52.23^\circ 2\theta$, comprising 291 reflections. The structure was refined against data in the range 7.5 to $60.0^\circ 2\theta$ (430 reflections). The restraints were set such that bonds and angles did not deviate more than 0.01 \AA and 1° , respectively, from their initial values during the refinement. Atoms C1, C2, C4, C5, C6, C7, H4, H7, C11 and S2 of HCT were restrained to be planar, as were atoms C8, C9, C10, O5 and O6 of the methyl acetate. The SA structure solution involved the optimization of one molecule of HCT plus one molecule of methyl acetate, totaling 13 degrees of freedom (six positional, six orientational and one torsional). All degrees of freedom were assigned random values at the start of the simulated annealing. The best SA solution had a favourable $\chi^2_{\text{SA}} / \chi^2_{\text{Pawley}}$ ratio of 5.2, a chemically reasonable packing arrangement and exhibited no significant misfit to the data. Prior to Rietveld refinement, atoms H31 and H32 (attached to N3) were set to positions which satisfied the hydrogen-bonding contacts within the structure. The solved structure was subsequently refined against data in the range 7.5 – $60.0^\circ 2\theta$ using a restrained Rietveld method (Rietveld, 1969) as implemented in *TOPAS* (Coelho, 2003), with the R_{wp} value falling to 0.0182 during the refinement. All atomic positions (including H atoms) for the structure of (I) were refined, subject to a series of restraints on bond lengths, angles and planarity. A spherical harmonics (8th order) correction of intensities for preferred orientation was applied in the final refinement (Järvinen, 1993). The observed and calculated diffraction patterns for the refined crystal structure are shown in Fig. 4. The atomic coordinates for all atoms are

taken from the software, and it is worth noting that the s.u. values derived from the Rietveld refinement are, in common with the majority of Rietveld refinements, significantly underestimated.

Data collection: *DIFFRAC* plus *XRD Commander* (Kienle & Jacob, 2003); cell refinement: *TOPAS* (Coelho, 2003); data reduction: *DASH* (David *et al.*, 2001); program(s) used to solve structure: *DASH*; program(s) used to refine structure: *TOPAS*; molecular graphics: *PLATON* (Spek, 2003); software used to prepare material for publication: *enCIFer* (Cambridge Crystallographic Data Centre, 2004).

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